REMARKS

The final Office Action mailed on May 5, 2008 is acknowledged. Applicant requests examination of the above-mentioned application in view of the following remarks.

I. Claims

Claims 1, 3, 5, 6-13 and 15-33 are pending in this application. In this Amendment, claims 6-8 are canceled according to the Examiner's suggestions. Also, claims 9 and 32-33 have been amended. Upon entry of these amendments, claims 1, 3, 5, 9-13, and 15-33 will be pending for examination. No new matter has been added.

II. Rejections

The only pending rejections are under 35 USC § 112 1st paragraph. Specifically, the Examiner alleges that the claims are non-enabled and lack adequate written description on the grounds stated in the prior Office Action of October 25, 2007. Applicants respectfully note, however, that the Examiner has not specified which claims are rejected.

Furthermore, applicants note that claim 5 was not rejected as non-enabled or lacking adequate written description in the Examiner's prior Office Action of October 25, 2007. Accordingly, applicants respectfully requests notification that claim 5 is deemed allowable. Applicants further respectfully traverse the non-enablement and lack of adequate written description rejections based on the data shown below obtained by applicants. The data shows various species covered by the pending claims and the activity of these species as kinase inhibitors.

Pharmacological Report

Receptor Inhibition Assays

The assays were performed according to the methods described below or in slight modifications thereof:

Tie-2 kinase assay:

The kinase assay is conducted in 96-well Flashplates. 150 ng Tie2 and 500 ng poly-Glu-Tyr (4:1) in a total volume of 100 µl (50 mM Hepes/NaOH, 0.1 µM ATPgammaS, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na_3VO_4, 1.85 mM Dithiothreithol, pH7.5), containing 0.3 µCi ^{33}P-ATP and 2.5 µg PEG20000 per well were incubated with or without test compound for 120 minutes at room temperature.

The reaction was stopped with 180 µl/well 2.5 % orthophosphoric acid. After 30 minutes at room temperature liquid was removed. Each well was washed thrice with 300 µl 0.9 % NaCl-solution. Non-specific reaction (blank) was determined with 10 µM of a proprietary kinase inhibitor. Radioactivity was measured with a topcount. IC_{50}-values were calculated in RS1.

VEGFR-2 Tyrosine-kinase assay

The kinase assay is conducted in 96-well Streptavidine-coated Flashplates. 10 ng VEGFR2 and 100 ng biotinylated poly-Glu-Tyr (4:1) in a total volume of 100 µl (50 mM Hepes/NaOH, 1 µM ATPgammaS, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na_3VO_4, 1.85 mM Dithiothreithol, pH7.5), containing 0.3 µCi ^{33}P-ATP and 2.5 µg PEG20000 per well were incubated with or without test compound for 120 minutes at room temperature.

The reaction was stopped with 180 µl/well 60 mM EDTA. After 30 minutes at room temperature liquid was removed. Each well was washed thrice with 300 µl 0.9 % NaCl-solution. Non-specific reaction (blank) was determined with 10 µM of a proprietary kinase inhibitor. Radioactivity was measured with a topcount. IC_{50}-values were calculated in RS1.

C-Raf Kinase Assay

The kinase assay is conducted in 96-well Streptavidine-coated Flashplates.

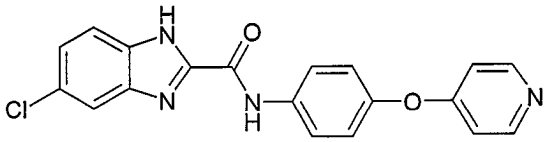
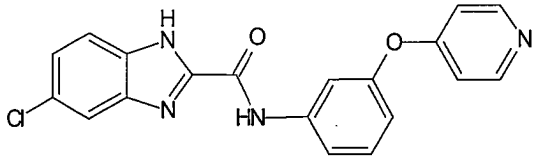
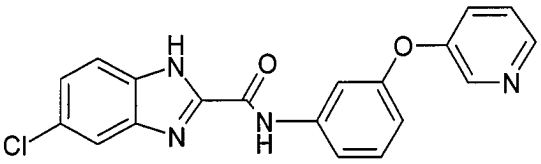
12.5 ng GST-cRaf, 250 ng biotinylated MEK and 1 µM ATP (containing 0.3-0.5 µCi ^{33}P-ATP/well) were incubated in a total volume of 100 µl (25 mM Tris-HCl, 5 mM □Glycerophosphate, 2 mM Dithiothreithol, 0.1 mM Na_3VO_4, 10 mM $MgCl_2$, 0.1% BSA, pH7.5)with or without test compound for 180 minutes at 30 °C.

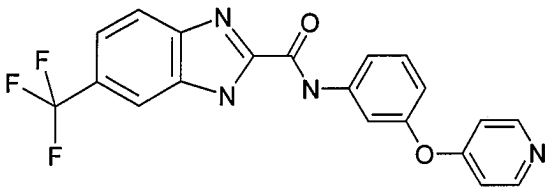
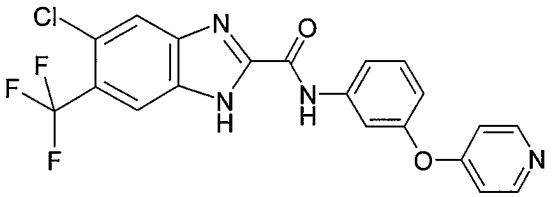
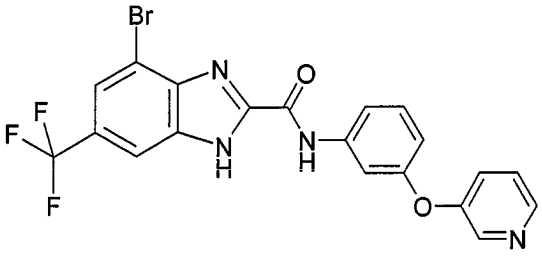
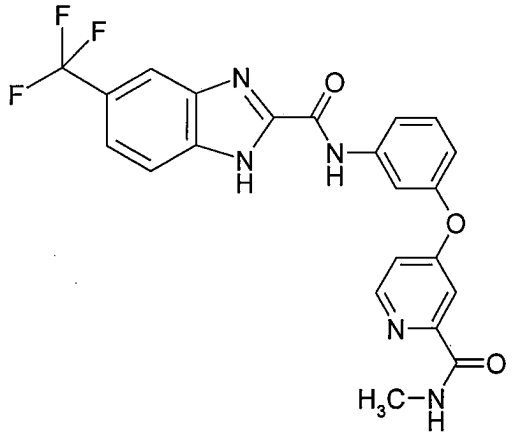
The reaction was stopped with 100 µl/well 100 mM EDTA. After 30 minutes at room temperature liquid was removed. Each well was washed thrice with 200 µl 0.9 % NaCl-solution. Non-specific reaction (blank) was determined with 10 µM of a proprietary kinase inhibitor. Radioactivity was measured with a topcount. IC_{50}-values were calculated in RS1.

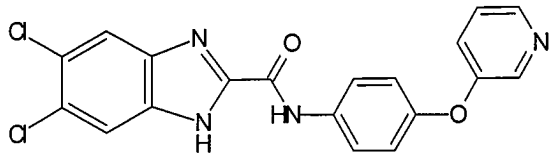
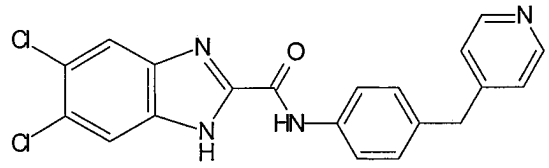
The data given in Table I shows that the compounds according to the invention are potent inhibitors of Raf kinase, and furthermore very potent inhibitors of VEGFR2 kinase.

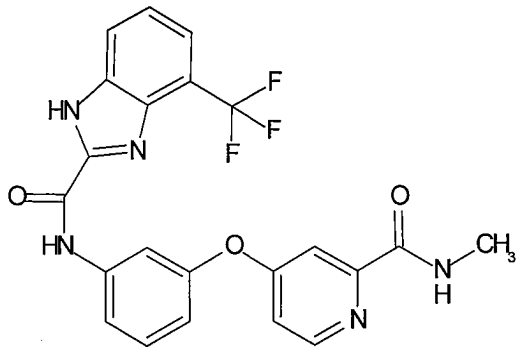
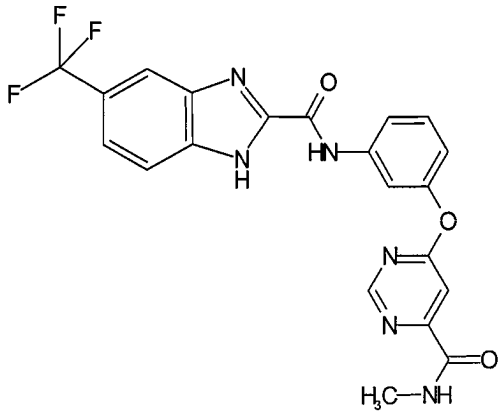
Table I

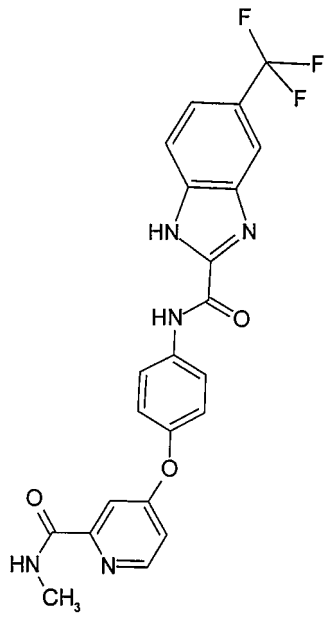
Structure, Molar Weight, HPLC Retention times and IC_{50} values of test compounds in the respective assays:

Structure	MW	R_t (min)	Tie-2 (IC_{50}) [mol/l]	VEGFR2 (IC_{50}) [mol/l]	Raf (IC_{50}) [mol/l]
	364,79	1,87	1,20E-05		
	364,79	1,89	5,10E-06		
	364,79	2,27	4,70E-06		

	398,34	2,05		9,10E-06	1,30E-07
	432,79	2,19			2,00E-06
	477,24	2,65	4,11E-06		
	455,4	2,67			2,20E-08

	399,24	2,42	3,00E-06		
	397,27	2,09			

	455,4	2,57			1,30E-06
	456,39	3.33c			4,40E-08

	455,4	2,59			3,80E-07

:

HPLC Method:
Gradient: 5.5 min; Flow: 2.75ml/min from 90:10 to - 0:100 H_2O/Acetonitrile
Water + TFA(0.01%Vol.); Acetonitrile + TFA(0.01%Vol.)
Column: Chromolith SpeedROD RP 18e 50-4.6
Wavelength: 220nm

[c]HPLC Method:
Gradient: 5.5 min; Flow: 2.75ml/min from 100:0 to - 0:100 H_2O/Acetonitrile
Water + TFA(0.01%Vol.); Acetonitrile + TFA(0.01%Vol.)
Column: Chromolith SpeedROD RP 18e 50-4.6
Wavelength: 220nm

Accordingly, in view of the above, applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections.

III. Conclusion

In view of the above amendments and remarks, notification of a favorable consideration is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below to expedite prosecution.

The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-3380, referencing Attorney Docket No. 978725.6/MPG-P0005.

Respectfully submitted,

BAKER & DANIELS, LLP

By 

Ronald J. Kamis, Reg. No. 41,104
Baker & Daniels LLP
805 15th Street, N.W., Suite 700
Washington, D.C. 20005
Telephone: (202) 312-7029
Facsimile: (202) 312-7441

RJK/lhr